# Physical Activity in Pediatric Pulmonary Arterial Hypertension Measured by Accelerometry

ORIGINAL ARTICLE

# Physical Activity in Pediatric Pulmonary Arterial Hypertension Measured by Accelerometry

## A Candidate Clinical Endpoint

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## Abstract

**Rationale:** The development of evidence-based treatment guidelines for pediatric pulmonary arterial hypertension (PAH) is hampered by lack of pediatric clinical trials. Trial design is hampered by lack of a feasible clinical endpoint in this population.

**Objectives:** To evaluate the use of accelerometry for measuring physical activity (PA) in pediatric PAH and to investigate its correlation with clinical disease severity markers.

**Methods:** We included children from the Dutch National Network for Pediatric Pulmonary Hypertension. Control patients were recruited from the outpatient cardiology clinic of the Beatrix Children's Hospital. Children were asked to wear the accelerometer for 7 days. Vector magnitude counts per minute (VM CPM) and time per day spent in different PA intensity levels were defined as accelerometer outcomes.

**Measurements and Main Results:** VM CPM was lower in children with PAH (n = 29) than in controls (n = 60; 647 vs. 921; $P < 0.001$). Children with PAH spent less time in moderate and vigorous PA (13 vs. 29 min/d and 2 vs. 13 min/d, respectively; $P < 0.001$). Time spent in moderate and vigorous PA correlated inversely with World Health Organization functional class. Time spent in moderate PA correlated positively with 6-minute-walk distance. In *post hoc* analyses, VM CPM and time spent in moderate/vigorous combined and vigorous PA were associated with outcome ($P \leq 0.044$).

**Conclusions:** PA is markedly decreased in children with PAH. Accelerometer output correlated with clinical disease severity markers and may predict outcome. We showed an exciting potential of PA as a meaningful endpoint for clinical trials in pediatric PAH, although its clinical utility and prognostic value need to be further validated.

**Keywords:** pulmonary arterial hypertension; pediatrics; physical activity; accelerometry

Pulmonary arterial hypertension (PAH) is a rare, progressive disease of the small pulmonary arteries and has a poor prognosis. Randomized controlled trials (RCTs) have led to significant advances and the development of treatment guidelines for adult PAH, resulting in improved quality of life and survival in adults with PAH (1).

In pediatric PAH, however, such advances are delayed, and prognosis remains unfavorable (2–5). In the United States, none, and in Europe only one, of the currently available PAH-targeted drugs are approved for children. The development of evidence-based treatment guidelines is hampered by the lack of RCTs in the pediatric age group. One essential problem in the design of RCTs in pediatric PAH is the definition of validated clinically meaningful endpoints or surrogate

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## At a Glance Commentary

**Scientific Knowledge on the Subject:** To date, the development of treatment guidelines for pediatric pulmonary arterial hypertension (PAH) guided by evidence-based treatment efficacy is hampered by the virtual lack of randomized controlled trials (RCTs) in this population. A major reason for this lack is the difficulty of defining a clinically meaningful and validated endpoint in infants and young children with PAH. Accelerometer output has been proposed as a potential endpoint in pediatric PAH, but data on the value of accelerometry in pediatric PAH are currently unavailable.

**What This Study Adds to the Field:** This study shows that physical activity measured by accelerometry is markedly decreased in children with PAH compared with in healthy control patients. Furthermore, accelerometer output correlated with clinical markers of disease severity and may also predict outcome. Accelerometer output directly reflects how a patient functions and could serve as a clinically meaningful endpoint in RCTs for pediatric PAH. Further validation in a second, larger population of children with PAH is warranted.

endpoints applicable in the pediatric age spectrum (6). Death may be considered a robust endpoint, as improving survival is a main objective in the treatment of PAH. However, such an endpoint is associated with significant ethical and practical problems (including the need for long study duration and large sample size). Given the rareness and poor prognosis of (pediatric) PAH, mortality trials are neither feasible nor preferable (7, 8).

In adults, the 6-minute-walk distance (6MWD) has served as primary endpoint in most pivotal clinical trials evaluating the efficacy of PAH-targeted drugs (9–11). In children, its use has been debated because the test cannot be reliably performed in young children or in children with developmental delays. Currently reported data on the value of the 6MWD in pediatric PAH regarding the assessment of disease severity and prognosis are contradictory, which seems related to the selection of children (2, 12–14). To date, no validated endpoints are available in young children with PAH, and therefore this is a high unmet need.

Accelerometry has been proposed as a potential endpoint in pediatric PAH, also because of its feasibility in young children (8, 15). It has been frequently used to measure physical activity (PA) in numerous clinical settings in both adults and children, including various cardiopulmonary diseases, and has been shown to correlate with peak oxygen consumption (16–19). Recently, accelerometer output has been reported to correlate with measurements of exercise tolerance in adult patients with PAH (20, 21).

To date, data regarding PA measured by accelerometry in children with PAH are lacking. In this study, we evaluated the value of accelerometry in pediatric PAH by comparing PA measured by accelerometry in children with PAH with that in healthy controls. Furthermore, we assessed whether accelerometer output correlates with disease severity and outcome in children with PAH.

## Methods

This is a prospective, observational study within the Dutch National Network for Pediatric Pulmonary Hypertension (22) and controls. The Medical Ethics Review Board of the University Medical Center Groningen waived the need for ethical approval. All subjects and/or their guardians gave written informed consent. In all included patients, PAH had been confirmed with cardiac catheterization, and patients were classified according to the Updated Clinical Classification of PAH, Nice, France, 2013 (23, 24).

### Patients and Controls

Children with PAH who visited the outpatient clinic of the National Referral Center for Pulmonary Hypertension in Childhood between June 2013 and March 2016 were asked to wear the ActiGraph wGT3X accelerometer (Pensacola, FL). Children with muscular diseases were excluded.

Patient characteristics, World Health Organization Functional Class (WHO-FC), 6MWD (in children $\geq$7 yr of age), and serum levels of N-terminal pro brain natriuretic peptide (NT-proBNP) were assessed. The 6-minute-walk test was conducted as previously reported (12, 25). 6MWD was presented as both absolute values and percentage of predicted (26). In one child with spondyloepiphyseal dysplasia, the 6-minute-walk test was regarded as unreliable, and therefore the test result was not used in the analyses. Data on medication use were also collected: calcium channel blocker therapy or PAH-targeted mono-, dual, or triple therapy.

For every child with PAH, two controls matched by age and sex were recruited from children who visited the outpatient pediatric cardiology clinic of the Beatrix Children's Hospital for screening for cardiac diseases but who appeared to have no, or no hemodynamically relevant, cardiac disease.

### Accelerometry

Children were instructed to wear the accelerometer for 7 consecutive days on the right hip during all awake time, except for during water-related activities. The accelerometer was programmed to record triaxial data at a frequency of 60 Hz. Data were processed using the ActiLife software (ActiGraph). Data were downloaded and integrated into 15-second epochs. Nonwear periods were defined as consecutive zeroes for $\geq$90 minutes, with a two-spike tolerance (27). Days with $\geq$8 hours of accelerometer wear were considered valid. In infants who still slept during the day, and consequently were awake for only 6–8 hours, days with $\geq$6 hours of accelerometer wear were considered valid. For inclusion in the analyses, patients were required to have $\geq$4 valid days.

Vector magnitude (VM) counts per minute (CPM) was defined as the primary accelerometer outcome. The VM is the square root of the quadrate of the three separate dimensional axes $[(x^2 + y^2 + z^2)^{1/2}]$. The total accelerometer VM counts were divided by the total number of minutes the device was worn to calculate VM CPM. PA intensity was defined as secondary accelerometer outcome and classified into sedentary, light, moderate, and vigorous PA, using cutpoints for the vertical axis as defined by Evenson and colleagues (28, 29).

### Statistics

Data are presented as mean (SD), median (interquartile range), or number (percentage). Statistical analysis was

conducted using IBM SPSS 22.0 (Armonk, NY) and R package (for partial Spearman correlation coefficients). Independent Student's *t* test, Mann-Whitney *U* test, chi-square test, or Fisher's exact test were used to compare data, as appropriate.

Pearson and Spearman correlation coefficients and linear regression analysis were used to evaluate the association between accelerometer output and clinical disease severity markers. For the sake of clinical interpretation, WHO-FC was taken as continuous variable in the linear regression analyses. Log-10 transformation was performed for serum levels of NT-proBNP to achieve normality. For the sake of clinical interpretation, log-2 transformation was performed for combined moderate/vigorous, moderate, and vigorous PA to achieve normality.

In post hoc outcome analyses, the first occurrence of death, lung transplantation, or nonelective PAH-related hospitalization was defined as the primary endpoint. Otherwise, children were censored at May 1, 2016. Freedom from events was depicted using a Kaplan-Meier curve. To explore whether accelerometer output predicted outcome, Cox regression analysis was performed.

*P* values of $<0.05$ were considered significant.

## Results

### Children with PAH

In total, 30 children with PAH were asked to wear an accelerometer. One 7-year-old child with Down syndrome refused to wear the accelerometer and was therefore excluded from the study.

Patient and disease characteristics of the remaining 29 children are shown in Table 1. There was a female predominance, and median age at diagnosis was 3.1 years. Median time between diagnosis and accelerometer study was 2.9 years (interquartile range, 0.9–11.7 yr). Four children (14%) were <5 years of age at the time of accelerometer study. Eight children (28%) wore the accelerometer within 1 year after diagnosis. Eleven children had idiopathic or hereditary PAH, 17 had PAH associated with congenital heart disease, and one had PAH associated with connective tissue disease. Three children had Down syndrome. Most children were in WHO-FC II or III. 6MWD was available in 19 children and not available in 9 children because of young age (<7 yr; n = 7) or developmental disorders (n = 2). Two children received calcium channel blocker therapy, and the remaining children received PAH-targeted therapies: eight monotherapy, 15 dual therapy, and five triple therapy.

Sixty age- and sex-matched controls were included in the study (Table 2). Controls visited the outpatient pediatric cardiology clinic for evaluation of a cardiac murmur, palpitations, or cardiac screening in the context of familial history of cardiomyopathy or arrhythmia. Hemodynamic significant heart diseases were excluded in all. Diagnoses included no cardiac abnormality (n = 57), trivial valve abnormalities (n = 1), and hemodynamic irrelevant shunt defects (small ventricular septal defect [n = 1] and mini silent patent ductus arteriosus [n = 1]).

**Table 1.** Patient and Disease Characteristics of the Children with PAH

| Characteristics | All Children with PAH *(N = 29)* |
|---|---|
| Age of diagnosis, yr | 3.1 (1.2–9.7) |
| Female | 19 (66) |
| Down syndrome | 3 (10) |
| Diagnosis | |
| IPAH/HPAH | 11 (38) |
| PAH-CHD | 17 (59) |
| PAH-CTD | 1 (3) |
| WHO-FC | |
| I | 4 (14) |
| II | 15 (52) |
| III | 9 (31) |
| IV | 1 (3) |
| 6MWD*, m; %pred* | 411 ± 68; 61.6 ± 10.0 |
| NT-proBNP, ng/L† | 160 (92–350) |
| PAH therapy | |
| CCB monotherapy | 2 (7) |
| PAH-targeted monotherapy | 8 (27) |
| PAH-targeted dual therapy | 15 (50) |
| PAH-targeted triple therapy | 5 (17) |

*Definition of abbreviations*: %pred = percentage of predicted; 6MWD = 6-minute-walk distance; CCB = calcium channel blocker; IPAH/HPAH = idiopathic or hereditary pulmonary arterial hypertension; NT-proBNP = N-terminal pro brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; WHO-FC = World Health Organization Functional Class.
Data are presented as median (interquartile range), number (percentage), or mean ± SD, as appropriate.
*6MWD available for 19 children.
†NT-proBNP available for 28 children.

**Table 2.** Physical Activity of Children with PAH and Controls

| Characteristics | Children with PAH *(n = 29)* | Controls *(n = 60)* | *P* Value |
|---|---|---|---|
| Age at test, yr | 12.0 (7.5–14.7) | 11.8 (9.0–15.1) | 0.878 |
| Female | 19 (66) | 38 (63) | 0.841 |
| BMI, kg/m$^2$ | 17.2 ± 2.6 | 18.0 ± 3.0 | 0.249 |
| VM CPM | 647 ± 274 | 921 ± 309 | <0.001 |
| Time in sedentary PA, h/d | 8.7 ± 2.0 | 8.3 ± 1.7 | 0.317 |
| Time in light PA, h/d | 3.5 ± 1.3 | 3.8 ± 0.9 | 0.250 |
| Time in MVPA, min/d | 13.3 (7.5–25.0) | 41.3 (31.9–54.9) | <0.001 |
| Time in moderate PA, min/d | 12.5 (4.8–20.9) | 29.2 (21.1–38.5) | <0.001 |
| Time in vigorous PA, min/d | 2.1 (0.8–4.4) | 13.4 (7.9–19.4) | <0.001 |

*Definition of abbreviations*: BMI = body mass index; MVPA = combined moderate/vigorous physical activity; PA = physical activity; PAH = pulmonary arterial hypertension; VM CPM = vector magnitude counts per minute.
Data presented as median (interquartile range), number (percentage), or mean ± SD, as appropriate.

### Physical Activity in Children with PAH and Controls

All included children wore the accelerometer for ⩾4 valid days and were included in the PA analyses. The majority of these children (89%) had 6 or 7 valid days, which did not differ between children with PAH and controls ($P = 0.642$). Mean wear time per valid day was 12.5 ± 1.7 hours for children with PAH and 12.8 ± 1.1 hours for controls ($P = 0.318$). There was no significant day-to-day variance in VM CPM (paired-samples $t$ tests; $P \geq 0.094$). During the weekend, children wore the accelerometer for a shorter time per day compared with weekdays (12.0 ± 1.6 vs. 13.0 ± 1.4 h/d; $P < 0.001$). However, no significant difference in VM CPM during week- or weekend days could be demonstrated (paired-samples $t$ test; $P = 0.641$).

Mean VM CPM was significantly lower in the children with PAH compared with in controls (Table 2 and Figure 1). Furthermore, children with PAH spent significantly less time per day in both moderate and vigorous activities compared with controls (Table 2 and Figure 2).

### Accelerometer Output in Pediatric PAH

Mean VM CPM did not differ between the 3 children with and the 26 children without Down syndrome (733 vs. 638; $P = 0.574$).

There was a significant correlation between age and VM CPM ($r = -0.495$; $P = 0.006$), and a considerably stronger correlation between age and time spent in sedentary ($r = 0.764$; $P < 0.001$) and light ($r = -0.466$; $P = 0.011$) PA. Time spent in moderate, vigorous, and combined moderate/vigorous PA did not correlate with age (data not shown). Children with associated PAH spent less time in vigorous PA than children with idiopathic PAH (IPAH; $r = -0.421$; $P = 0.023$ [reference category IPAH]). We could not demonstrate a correlation between accelerometer output and sex, body mass index, diagnosis, or NT-proBNP serum level (data not shown).

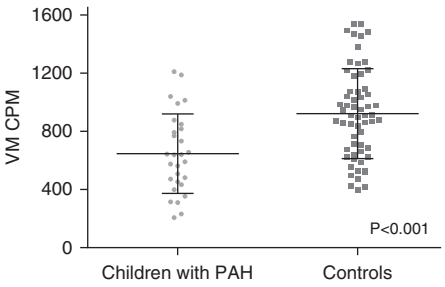


**Figure 1.** Vector magnitude counts per minute (VM CPM) for the children with pulmonary arterial hypertension (PAH) and controls. Showing all individual data for each group with mean and SD. Mean VM CPM was significantly lower in the children with PAH compared with controls (647 vs. 921 CPM, respectively; $P < 0.001$).

VM CPM correlated inversely with WHO-FC in the univariate analysis, but lost its significance when corrected for age and diagnosis (Table 3) Time spent in moderate, vigorous, and combined moderate/vigorous PA correlated inversely with WHO-FC, which did not change substantially after adjustment for age and diagnosis. Time spent in moderate, vigorous, and combined moderate/vigorous PA correlated positively with 6MWD, although with respect to time spent in vigorous PA, statistical significance did not remain after adjustment for age and diagnosis. We also tested for differences in regression coefficients between accelerometer outcomes and clinical disease severity markers in a univariate analysis and analysis adjusted for age and diagnosis (Table 4). The findings remained generally the same. In addition, similar correlation and regression coefficients were observed between the percentage of predicted 6MWD and time spent in moderate, vigorous, and combined moderate/vigorous PA.

### Outcome

During a median follow-up of 2.2 years, 3 children were nonelectively hospitalized for PAH-related reasons (i.e., progressive right heart failure). Two children subsequently died within weeks after admission. In none of the 29 children was intravenous or subcutaneous prostacyclin therapy initiated during the study period.

Post hoc Cox regression analysis revealed that lower VM CPM was significantly associated with a shorter time to event (Figure 3). Also, less time spent in more intense activity levels (combined moderate/vigorous PA or vigorous PA) was associated with worse outcome ($P = 0.036$ and $P = 0.044$, respectively).

## Discussion

This study is the first to demonstrate that PA measured by accelerometry is markedly decreased in children with PAH compared with controls, particularly moderate and vigorous PA. Furthermore, accelerometer output correlated considerably with clinical disease severity markers and outcome.

### Accelerometry in Pediatric PAH

In pediatric PAH, there is a high unmet need for an endpoint or a validated surrogate endpoint applicable in the pediatric age spectrum. A clinically meaningful endpoint should reflect how a patient feels, functions, or survives (30). Function refers to the ability of a patient to carry out normal daily activities. This is especially important in PAH, as exercise intolerance, reflected by dyspnea at exertion, increased WHO-FC, and impaired 6MWD and peak oxygen consumption, is one of the main features of PAH (1, 5, 23, 31). Children with PAH cannot keep up with their peers in participating in the normal daily activities of childhood, such as playing in the playground, running, dancing, or playing soccer, which greatly affects quality of life. In this study, we used accelerometry to objectively measure PA, and confirmed that PA is significantly decreased in children with PAH. As such, accelerometer output provides direct information on how a child with PAH functions. In this respect, accelerometer output is thus not a surrogate endpoint, with inherently required validation criteria, but constitutes a clinically meaningful endpoint.

Impaired exercise tolerance in PAH has been usually evaluated using 6MWD. Recently, a study in the Dutch cohort of pediatric patients with PAH showed that the 6MWD is an independent predictor of prognosis in children ⩾7 years of age and reflects disease severity and exercise tolerance in daily life (12). The current study demonstrates that accelerometer output correlates with 6MWD, confirming the clinical relevance of this measurement. This correlation has also been reported in adults with PAH (20, 21). A well-established limitation of the 6-minute-walk test is that it cannot be reliably performed in young children or in children with severe mental or physical disabilities. Furthermore, it can be influenced by non-PAH-related factors such as motivation of the child and guidance during the test. In contrast, accelerometry provides an objective measurement of PA and can be reliably performed in children of all ages, regardless of any disabilities. Therefore,

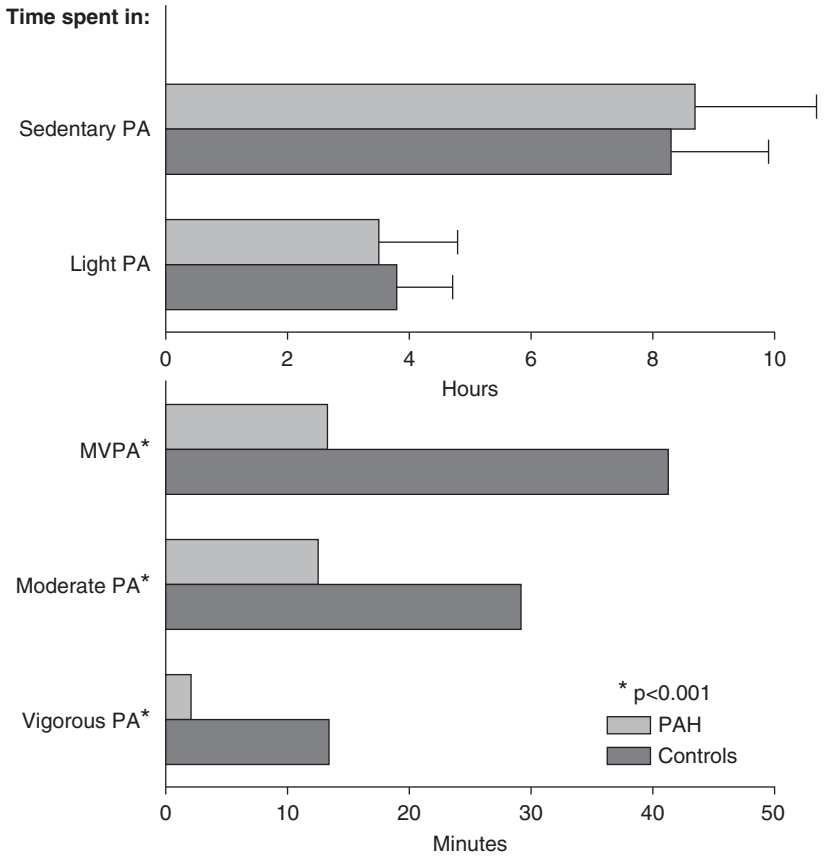


**Figure 2.** Physical activity (PA) intensity levels for the children with pulmonary arterial hypertension (PAH) and controls. Showing mean and SDs of hours per day spent in sedentary and light PA and median minutes per day spent in moderate/vigorous PA (interquartile range for children with PAH, 7.5–25.0; for controls, 31.9–54.9), moderate PA (interquartile range for children with PAH, 4.8–20.9; for controls, 21.1–38.5), and vigorous PA (interquartile range for children with PAH, 0.8–4.4; for controls, 7.9–19.4) for the children with PAH and controls. *$P < 0.001$. MVPA = moderate/vigorous physical activity.

accelerometry could be a good alternative to evaluate exercise tolerance in children who cannot (reliably) perform a 6-minute-walk test.

Another well-established clinical parameter for disease severity is the WHO-FC, a subjective assessment of a patient's clinical condition using the occurrence of symptoms at different levels of PA. Its value in infants and young children has been debated, as it is based on the observation and impression of caregivers and/or the treating physician. Nevertheless, WHO-FC also has been shown to be a strong and independent predictor of prognosis in pediatric PAH (13, 32). In addition, changes in WHO-FC were recently shown to predict survival (33). In this study, accelerometer output correlated with WHO-FC, which further supports the value of accelerometry in assessing exercise tolerance in pediatric PAH.

In this cross-sectional study, accelerometer output did not correlate with single time-point measurements of NT-proBNP serum level. Although single time-point measurements of NT-proBNP have been shown to predict outcome in pediatric PAH, its major strength is that changes in NT-proBNP serum levels during follow-up predict (changes in) outcome (33). As such, NT-proBNP qualifies as a surrogate endpoint and may serve as a treatment goal in pediatric PAH. Accelerometer output, however, reflecting how a patient feels and functions, constitutes a clinically meaningful endpoint in itself. Although both measurements are affected by the disease PAH, and both may predict outcome in pediatric PAH, they represent two different features of PAH, that is, myocardial load versus stamina, and it is not clear whether the mechanisms by which both measurements are affected by the disease are the same. This also accounts for other proposed endpoints, including biomarkers, echocardiographic parameters, and hemodynamics. Therefore, the absence of a one-on-one correlation between accelerometer output and such endpoints does not diminish the value of either of them, nor of accelerometry as a clinically meaningful endpoint in pediatric PAH. Further research is needed to establish whether changes in NT-proBNP serum levels over time correlate with changes in accelerometer output.

A major advantage of accelerometry over these other proposed endpoints is that it is a direct, objective, noninvasive, and relatively cheap measurement. Furthermore, accelerometry appeared to be feasible in children of all ages. Of 30 children, in only one child with Down syndrome did accelerometry appear not feasible, as a result of noncompliance. Biomarkers, echocardiographic parameters, and hemodynamics do not directly reflect how a patient feels, functions, or survives. However, these measurements may carry prognostic value and could qualify as surrogates for outcome (7, 34). To date, their use as surrogates remains to be validated. In addition, the assessment of hemodynamics requires the need for invasive measurement, as these are obtained during cardiac catheterization, bringing along certain risks, and often the need for sedation or anesthesia (35, 36).

In a post hoc analysis, accelerometer output predicted outcome, defined as the first occurrence of death, lung transplantation, or hospitalization. It must be noted that only three events occurred, and all consisted of nonelective PAH-related hospitalizations. Reason for hospitalization was progressive right heart failure, and two children died within weeks after hospitalization. Although these results suggest that accelerometer output is of prognostic value in pediatric PAH, this study does not allow for definitive conclusions in this respect. Further research is needed to further establish the value of accelerometry as a prognostic tool.

### PA in Children with PAH

There may be various explanations for the markedly decreased PA in children with PAH. First, the PAH itself, resulting in decreased cardiac output, could very well cause exercise intolerance, resulting in decreased PA. Children with associated

**Table 3.** Correlations of Clinical Disease Severity Markers and Accelerometer Output

| | WHO Functional Class | | | | 6MWD | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Adjusted for Age and Diagnosis | | Univariate | | Adjusted for Age and Diagnosis | |
| | *r* | *P* Value | *r* | *P* Value | *r* | *P* Value | *r* | *P* Value |
| VM CPM | −0.369 | 0.049 | −0.266 | 0.233 | 0.221 | 0.363 | | |
| Sedentary PA | 0.269 | 0.119 | | | 0.002 | 0.993 | | |
| Light PA | −0.282 | 0.138 | | | 0.282 | 0.242 | | |
| MVPA | −0.398 | 0.002 | −0.380 | 0.053 | 0.521 | 0.022 | 0.429 | 0.085 |
| Moderate PA | −0.371 | 0.048 | −0.356 | 0.085 | 0.585 | 0.009 | 0.530 | 0.029 |
| Vigorous PA | −0.466 | 0.015 | −0.445 | 0.022 | 0.456 | 0.050 | 0.317 | 0.215 |

*Definition of abbreviations*: 6MWD = 6-minute-walk distance; MVPA = combined moderate/vigorous physical activity; PA = physical activity; VM CPM = vector magnitude counts per minute; WHO = World Health Organization.

PAH spent even less time in vigorous PA than children with IPAH. This group mostly included children with PAH associated with congenital heart disease and shunt defects (n = 14). Such children may not be able to reach a vigorous PA intensity level because of cyanosis that develops or aggravates during exercise. Second, it may be that PA is restricted by the caregivers/parents (or the children with PAH themselves) because of concerns and fear for adverse effects of PA, such as dyspnea, syncope, or sudden death. Chronic restriction of PA will lead to decreased fitness and decreased muscle strength. The latter was recently shown in adult patients with PAH (37). Such fears might have been enhanced by the fact that exercise training (i.e., moderate or vigorous PA) has long been believed to be harmful in patients with PAH (38). However, this point of view is changing, and with the improved therapeutic options for PAH, exercise training is now regarded to be safe (1). Moreover, several studies in adults with PH showed that exercise training improved exercise capacity, 6MWD, WHO-FC, quality of life, and peak oxygen consumption and led to higher levels of PA (measured by questionnaires) and decreased levels of fatigue (39–41). Future research, aiming at improving quality of life, could be directed toward evaluating muscle strength and the value of exercise programs also in pediatric PAH. Accelerometry could be used as a tool to guide such programs and monitor efficacy.

**Table 4.** Regression Coefficients of Accelerometer Outcomes and Clinical Disease Severity Markers

| Predictive Value | Univariable | | Adjusted for Age and Diagnosis | |
|---|---|---|---|---|
| | B (95% CI) | *P* Value | B (95% CI) | *P* Value |
| VM CPM | | | | |
| WHO-FC | −0.1 (−0.2 to 0.0) | 0.065 | −0.1 (−0.2 to 0.1) | 0.314 |
| 6MWD, m | 6 (−8 to 21) | 0.363 | 7 (−12 to 26) | 0.442 |
| Sedentary PA, h/d | | | | |
| WHO-FC | 0.1 (0.0 to 0.2) | 0.121 | 0.0 (−0.2 to 0.2) | 0.771 |
| 6MWD, m | 0 (−18 to 19) | 0.993 | 3 (−23 to 28) | 0.835 |
| Light PA, h/d | | | | |
| WHO-FC | −0.2 (−0.4 to 0.0) | 0.075 | −0.12 (−0.4 to 0.1) | 0.229 |
| 6MWD, m | 17 (−13 to 48) | 0.242 | 32 (0 to 64) | 0.050 |
| MVPA, min/d | | | | |
| WHO-FC | −0.2 (−0.4 to 0.0) | 0.038 | −0.2 (−0.4 to 0.0) | 0.040 |
| 6MWD, m | 24 (4 to 44) | 0.022 | 20 (−3 to 44) | 0.085 |
| Moderate PA, min/d | | | | |
| WHO-FC | −0.2 (−0.4 to 0.02) | 0.047 | −0.2 (−0.4 to 0.0) | 0.062 |
| 6MWD, m | 29 (8 to 49) | 0.009 | 26 (3 to 48) | 0.029 |
| Vigorous PA, min/d | | | | |
| WHO-FC | −0.2 (−0.3 to 0.0) | 0.038 | −0.2 (−0.3 to 0.0) | 0.026 |
| 6MWD, m | 17 (0 to 34) | 0.050 | 13 (−9 to 35) | 0.215 |

*Definition of abbreviations*: 6MWD = 6-minute-walk distance; CI = confidence interval; MVPA = combined moderate/vigorous physical activity; PA = physical activity; VM CPM = vector magnitude counts per minute; WHO-FC = World Health Organization Functional Class.
B represents the increase or decrease in WHO-FC or 6MWD per 100 increase in VM CPM, hours per day spent in sedentary and light PA, and per doubling of minutes per day spent in MVPA, moderate PA, and vigorous PA.

### Strengths, Limitations, and Future Directions

As validated endpoints are currently lacking in pediatric PAH, the results of this proof-of-concept study form an important base for the validation of accelerometer output as a clinically meaningful endpoint. Nevertheless, further validation of this potentially valuable endpoint is warranted. Its use should be evaluated in a second, larger cohort, preferably including a larger proportion of children <5 years of age and infants. Accelerometry has been previously validated in young children in other conditions, supporting its use also in the very young ones (18). A potential disadvantage of the use of accelerometry in infants children may be that accelerometry cannot recognize when a child is carried by a caregiver. The use of diaries may overcome this limitation. The age distribution in our cohort, with predominantly patients older than 5 years of age, did allow for comparisons between accelerometer output and 6MWD.

Further aspects that need to be addressed to validate the use of accelerometry in pediatric PAH include investigating how PA levels measured by accelerometry change over time in this population, whether therapy effects can be detected, and the determination of a minimal clinically important change in PA. With respect to reproducibility, the

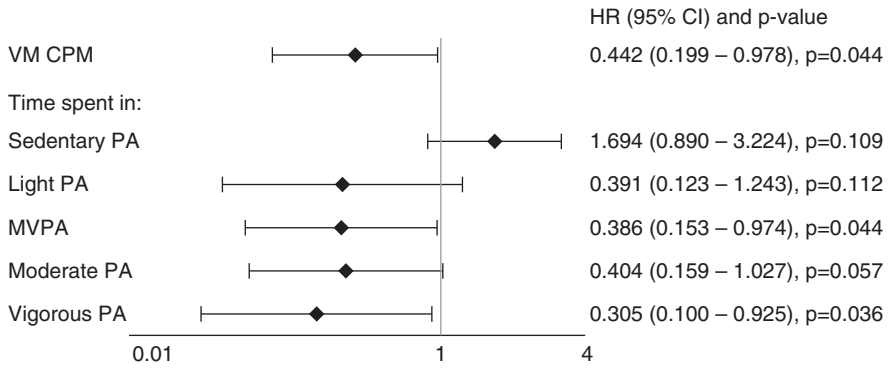


**Figure 3.** Predictive value of accelerometer outcomes for freedom of events. Forest plot showing hazard ratios with 95% confidence intervals. Hazard ratios per 100 increase in vector magnitude counts per minute (VM CPM), hours per day spent in sedentary and light physical activity (PA) and per doubling of minutes per day spent in combined moderate/vigorous physical activity (MVPA), or moderate or vigorous PA. Event was defined as nonelective pulmonary arterial hypertension–related hospitalization, lung transplantation, or death. CI = confidence interval; HR = hazard ratio.

accelerometer device used in the current study has been shown to have a good reproducibility in children, including in preschool children (42, 43). Although in the current study accelerometer output did not differ between weekdays and weekend days, it has been suggested that children are less active in the weekends than during weekdays (44). Also, there may be seasonal variation in children's physical activity (45). These remain topics for further investigation.

The children with PAH included in this study come from a national cohort with standardized diagnostic, follow-up, and treatment protocols. The inclusion of a matched control group provided the opportunity to directly compare PA between children with PAH and children without PAH. Complete and standardized follow-up in all children further enhanced the power of this study. In this study, we used the Evenson cutpoints for PA intensity levels, currently recommended to be used in children and adolescents (29). General consensus on such cutpoints is still to be achieved. The relatively small sample size is a limitation of this study, but is inherent to prospective studies in a rare disease as pediatric PAH.

## Conclusions

PA can be assessed objectively in children of various ages using accelerometry. Children with PAH have markedly decreased PA compared with healthy controls. In particular, time spent in higher PA intensity levels was severely reduced. Accelerometer output is associated with clinical disease severity independent from age and diagnosis and may also predict outcome. It provides an objective and direct measurement of how a patient functions. Therefore, accelerometer output could serve as a clinically meaningful endpoint for clinical trials in children with PAH. Further validation in a second, larger population of children with PAH is warranted. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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